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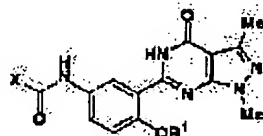
Priority number : 07 6986    Priority date : 20.01.1995    Priority country : JP

## (54) 1H-PYRAZOLO(3,4-D)PYRIMIDIN-4-ONE DERIVATIVE

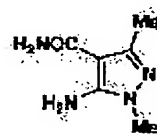
(57)Abstract:

PURPOSE: To provide a new derivative consisting of a specific 1H-pyrazolopyridin-4-one derivative, having cyclic GMP-specific phosphodiesterase inhibiting action and useful e.g. for the treatment of hypertension, myocardial infarction, atopic dermatitis, etc.

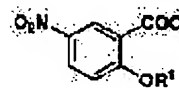
CONSTITUTION: This new 1H-pyrazolo[3,4-a]pyrimidin-4-one derivative is expressed by formula I [R<sup>1</sup> is a 1-4C alkyl; X is phenoxy or a group of R<sup>2</sup>R<sup>3</sup>N (R<sup>2</sup> and R<sup>3</sup> are each H or a 2-4C hydroxyalkyl); the group of formula R<sup>2</sup>R<sup>3</sup>N is morpholino, piperidino, pyrrolidino, thiazolino, etc.; Me is methyl]. It has a cyclic GMP-specific phosphodiesterase inhibiting action and is useful e.g. for the treatment of hypertension, stenocardia, cardiac insufficiency, myocardial infarction, arteriosclerosis, asthma, atopic dermatitis, allergic rhinitis, etc. The compound can be produced by reacting 5-amino-1H-pyrazole-4-carboxamide of formula II with a substituted benzoyl chloride of formula III, cyclizing the resultant compound of formula IV and acylating the product by reduction.



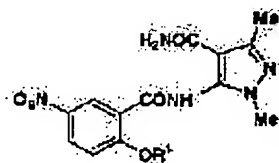
I



II



III



IV

LEGAL STATUS

[Date of request for examination] 17.12.2002

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[Date of final disposal for application]

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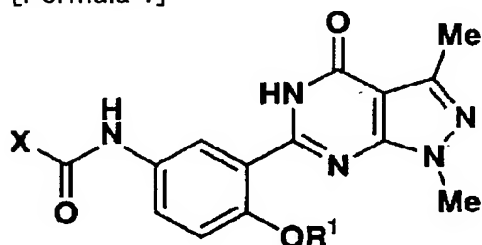
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## CLAIMS

[Claim(s)]

[Claim 1]

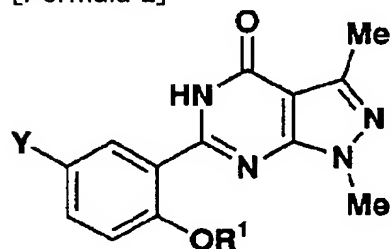
[Formula 1]



R1 shows the alkyl group of 1-4 carbon atomic numbers during the [-izing 1, and X shows a phenoxy group or an R2R3-N set. R2 and R3 are the same here -- or it differs, and a hydrogen atom or the hydroxyalkyl radical of 2-4 carbon atomic numbers is shown, or a morpholino radical, a piperidino radical, a pyrrolidino radical, a 4-hydroxy piperidino radical, 4-cull BETOKISHI piperidino radical, 4-carboxy piperidino radical, a thio morpholino radical, a thiazolino radical, or 4-methyl piperazino radical is shown as an Rtwo R3-N set.] The 1H-[3 and 4-pyrazolo d] pyrimidine-4-ON derivative come out of and expressed, and its salt.

[Claim 2]

[Formula 2]



[-- R1 shows the alkyl group of 1-4 carbon atomic numbers during-izing 2, and Y shows the amino group or a nitro group.] The 1H-[3 and 4-pyrazolo d] pyrimidine-4-ON derivative come out of and expressed, and its salt.

[Translation done.]

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## DETAILED DESCRIPTION

## [Detailed Description of the Invention]

[0001]

[Industrial Application] This invention relates to the 1H-[3 and 4-pyrazolo d] pyrimidine-4-ON derivative which has cyclic GMP specific phosphodiesterase inhibitory action.

[0002]

[Description of the Prior Art] Conventionally, the compound of EP No. 349239 is known as a cyclic GMP specific phosphodiesterase inhibitor which has the 1H-[3 and 4-pyrazolo d] pyrimidine frame. Moreover, although WO 93/No. 07149 has reported the compound which has strong cyclic GMP specific phosphodiesterase inhibitory action by introducing a substituent into the 5th place of the phenyl group of the 2nd place, there is no publication of the compound which has as a substituent the ureido radical shown by this invention.

[0003]

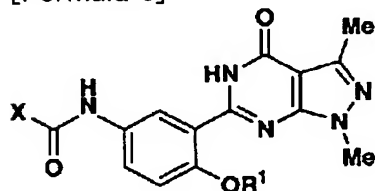
[Problem(s) to be Solved by the Invention] The purpose of this invention is to offer the compound which has strong cyclic GMP specific phosphodiesterase inhibitory action, as a result use for the therapy of hypertension, angina pectoris, cardiac insufficiency, myocardial infarction, arteriosclerosis, asthma, the chronic reversible drowned lung like bronchitis, atopic dermatitis, allergic rhinitis, etc.

[0004]

[Means for Solving the Problem] As a result of examining wholeheartedly the compound which has cyclic GMP specific phosphodiesterase inhibitory action, this invention persons found out that the compound which has a certain kind of 1H-[3 and 4-pyrazolo d] pyrimidine-4-ON frame filled the purpose concerned, and completed this invention based on the knowledge further.

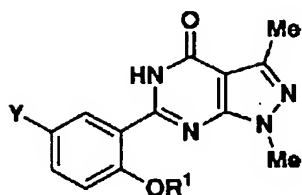
[0005] That is, this invention is [0006].

[Formula 3]



[0007] R1 shows the alkyl group of 1-4 carbon atomic numbers during the [-izing 3, and X shows a phenoxy group or an R2R3-N set. R2 and R3 are the same here -- or it differs, and a hydrogen atom or the hydroxyalkyl radical of 2-4 carbon atomic numbers is shown, or a morpholino radical, a piperidino radical, a pyrrolidino radical, a 4-hydroxy piperidino radical, 4-cull BETOKISHI piperidino radical, 4-carboxy piperidino radical, a thio morpholino radical, a thiazolino radical, or 4-methyl piperazino radical is shown as an Rtwo R3-N set.] The 1H-[3 and 4-pyrazolo d] pyrimidine-4-ON derivative come out of and expressed, its salt, and [0008]

[Formula 4]



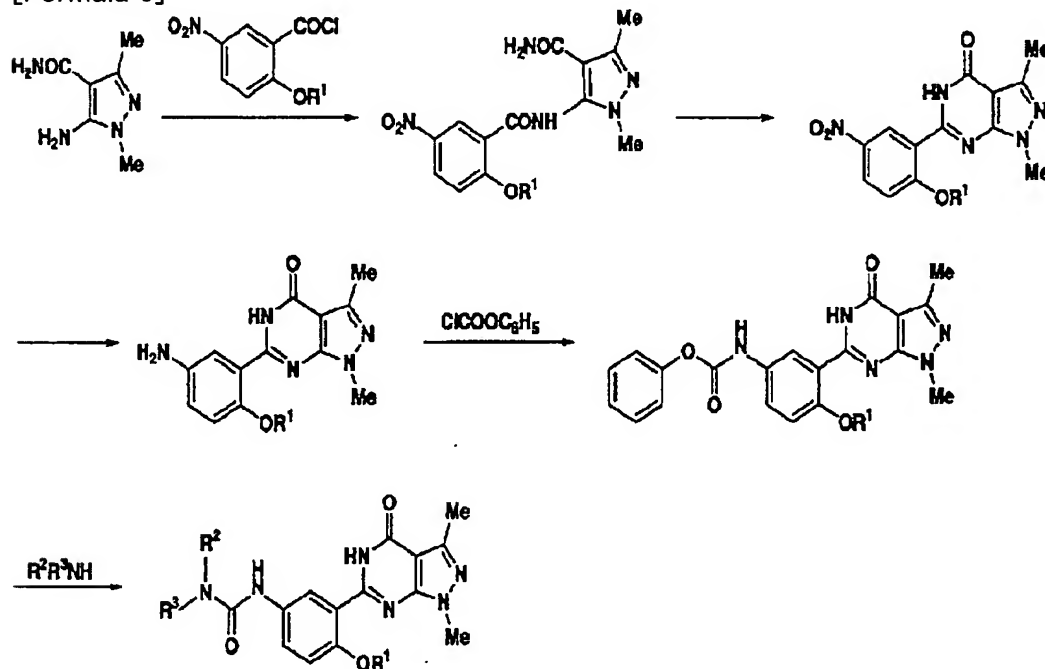
[0009] [-- R1 shows the alkyl group of 1-4 carbon atomic numbers during-izing 4, and Y shows the amino group or a nitro group.] It comes out and they are the 1H-[3 and 4-pyrazolo d] pyrimidine-4-ON derivative expressed and its salt.

[0010] In this invention, the alkyl group of 1-4 carbon atomic numbers means the alkyl group of the shape of the shape of a straight chain, such as a methyl group, an ethyl group, a propyl group, and an isopropyl group, and a branched chain. The hydroxyalkyl radical of 2-4 carbon atomic numbers means the monochrome or dihydroxy alkyl group of the shape of the shape of a straight chain, such as a 2-hydroxyethyl radical, 3-hydroxypropyl radical, 2-hydroxy-2-methylpropyl radical, 4-hydroxy butyl, 2, 3-dihydroxy propyl group, 1, and 3-dihydroxy-2-propyl group, and a branched chain.

[0011] The compound of this invention can be manufactured by the manufacture scheme shown in \*\* 5.

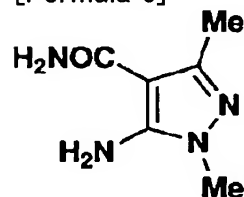
[0012]

[Formula 5]



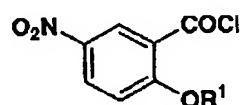
[0013] [-- they are R1, R2 and R3, \*\*\*\*\*, and this meaning during-izing 5.] 5-amino-1H-pyrazole-4-carboxamide expressed with \*\* 6 which is a start raw material [0014]

[Formula 6]



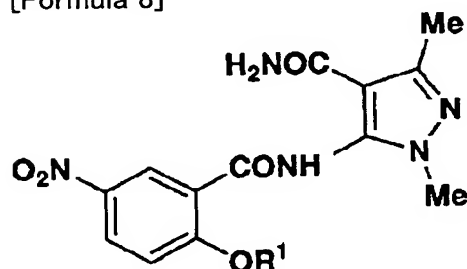
[0015] [0016]

[Formula 7]



[0017] [— R1 is the above and this meaning during-izing 7.] Come out, the compound expressed is made to react under base existence, and it is [0018].

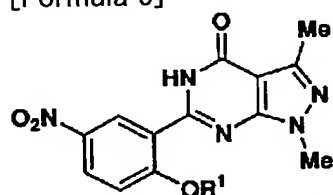
[Formula 8]



[0019] [— R1 is the above and this meaning during-izing 8.] It comes out and the compound expressed is obtained.

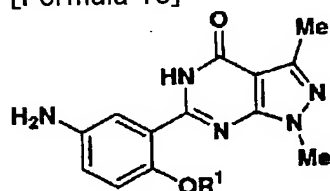
[0020] here, organic bases, such as triethylamine and a pyridine, can be used as a base, and independent [ in solvents such as N.N-dimethylformamide a tetrahydrofuran, an acetone, chloroform, and dichloromethane, ] as a reaction solvent — or it can mix and use. Reaction temperature is the reflux temperature from 0 degree C.

[0021] Subsequently, it is [0022] by processing the compound expressed with \*\* 8 by the base. [Formula 9]



[0023] [— R1 is the above and this meaning during-izing 9.] It is [0024] by coming out, obtaining the compound expressed and returning the nitro group of \*\* 9.

[Formula 10]



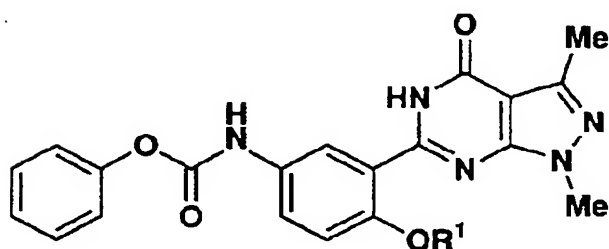
[0025] [— R1 is the above and this meaning during-izing 10.] It comes out and the compound expressed is obtained.

[0026] Here, as a base to be used, inorganic bases, such as a potassium hydroxide and a sodium hydroxide, can be used, and alcoholic solvent, such as a methanol and ethanol, can be used as a reaction solvent, and hydrogen peroxide solution can be added. Reaction temperature is the reflux temperature from a room temperature.

[0027] moreover, as a reducing agent, reducing agents, such as palladium carbon-hydrogen, a nickel chloride-sodium borohydride, and an iron-acetic acid, can be used, and independent [ in solvents such as a methanol, ethanol, a tetrahydrofuran, and an acetic acid ] as a reaction solvent — or it can mix and use. Reaction temperature is the reflux temperature from 0 degree C.

[0028] Subsequently, chloro formic acid phenyl is made to react to the compound expressed with \*\* 10 under base existence, and it is [0029].

[Formula 11]



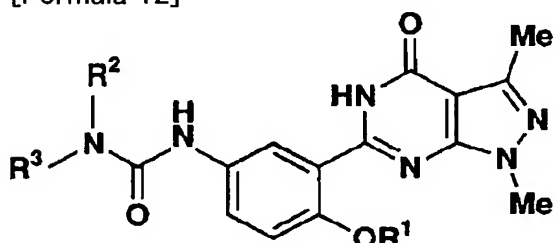
[0030] [— R1 is the above and this meaning during-izing 11.] It comes out and the compound expressed is obtained.

[0031] Here, organic bases, such as triethylamine and a pyridine, can be used as a base to be used, and solvents, such as N,N-dimethylformamide, a tetra-HIRODO furan, and an acetone, can be used as a reaction solvent. Reaction temperature is the reflux temperature from a room temperature.

[0032] Subsequently, the compound and the 1-5Eq formula (I) which are expressed with \*\* 11 R2R3NH (I)

R2 and R3 are the above and this meaning among the [type I. ] It is [0033] by coming out and making the amine expressed react.

[Formula 12]

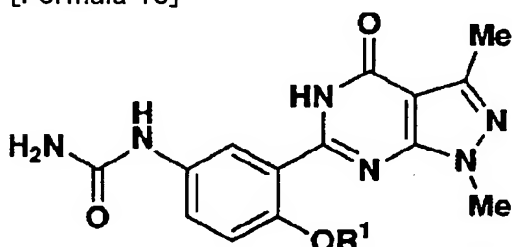


[0034] [— R1, R2, and R3 are the above and this meaning during-izing 12. ] It can come out and the compound expressed can be obtained.

[0035] Here, as a reaction solvent, solvents, such as N,N-dimethylformamide, a tetra-HIRODO furan, and an acetone, can be used. Reaction temperature is the reflux temperature from 0 degree C.

[0036] Moreover, [0037] R2 and whose R3 are hydrogen atoms in \*\* 12

[Formula 13]

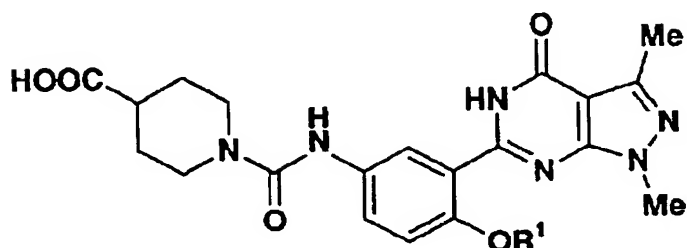


[0038] [— R1 is the above and this meaning during-izing 13.] It can come out and the compound expressed can be obtained under the compound and acid existence which are expressed with \*\* 10 by making 1-5Eq potassium cyanate or sodium cyanate react.

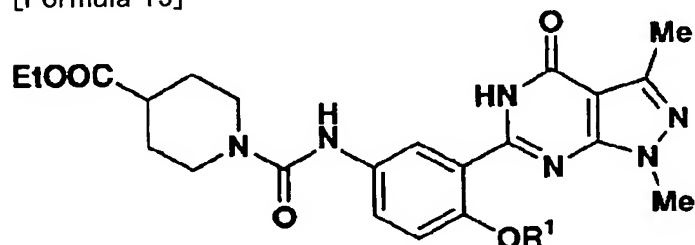
[0039] Here, organic acids, such as an acetic acid, can be used as an acid. independent [ in solvents, such as water and an acetic acid, ] as a reaction solvent -- or it can mix and use. Reaction temperature is the reflux temperature from 0 degree C.

[0040] Moreover, [0041] whose Rtwo R3-N set is 4-carboxy piperidino radical in \*\* 12

[Formula 14]



[0042] [— R1 is the above and this meaning during-izing 14.] The compound come out of and expressed is the bottom of base existence, and [0043].  
[Formula 15]



[0044] [— R1 is the above and this meaning during-izing 15.] It can obtain by coming out and hydrolyzing the compound expressed.

[0045] Here, as a base, inorganic bases, such as potassium carbonate, a sodium hydroxide, and a potassium hydroxide, can be used, and water, a methanol, ethanol, etc. can be used as a reaction solvent. Reaction temperature is the reflux temperature from a room temperature.

[0046]

[Effect of the Invention] The purpose of this invention has strong cyclic GMP specific phosphodiesterase inhibitory action, as a result is useful for the therapy of hypertension, angina pectoris, cardiac insufficiency, myocardial infarction, arteriosclerosis, asthma, the chronic reversible drowned lung like bronchitis, atopic dermatitis, allergic rhinitis, etc.

[0047]




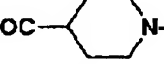


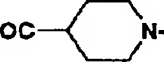


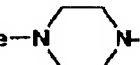

[Example] Hereafter, the example of reference and an example are given and this invention is further explained to a detail.

[0048] Moreover, the structure expression of the compound manufactured according to examples 1-23 is shown in Tables 1-3.

[0049]

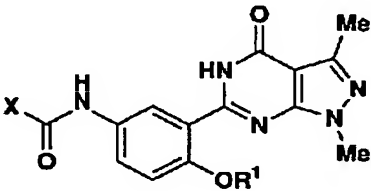
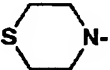

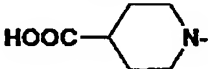
[Table 1]



構造式		
		
No.	R <sup>1</sup>	X
4	Pr	PhO
5	Pr	
6	Pr	
7	Pr	EtOOC- 
11	Et	PhO
12	Et	
13	Et	
14	Et	EtOOC- 
15	Et	
16	Et	(HOCH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> N-
17	Et	(HOCH <sub>2</sub> ) <sub>2</sub> CHNH-
18	Et	HO- 
19	Et	Me-N- 
20	Pr	

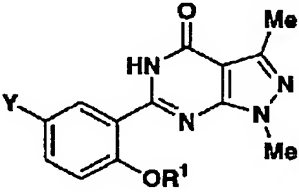
[0050]

[Table 2]

構造式		
		
No.	R¹	X
20	Pr	
21	Et	
22	Pr	H₂N-
23	Et	

[0051]

[Table 3]

構造式		
		
No.	R¹	Y
2	Pr	O₂N-
3	Pr	H₂N-
9	Et	O₂N-
10	Et	H₂N-

[0052] Example of reference 15-amino-4-cyano - The methanol 300ml solution (1 and 3-dimethyl-1H-pyrazole (1-ethoxy ethylidene) MARONO nitril 27.2g and methylhydrazine 9.2g (1.0Eq)) was flowed back for 3 hours. Reduced pressure distilling off of the solvent was carried out for the reaction solution after neglect overnight, and ethyl acetate was added, and the crystal was separated, it dried, and 17.84g of title compounds was obtained.

[0053] 3.44 (3H, s) 1 H-NMR(DMSO-d6)  $\delta$ ppm; 2.05 (3H, s), 6.44 (2H, bs).

[0054] The example of reference 25-amino - 1, 3-dimethyl-1H - Pyrazole-4-carboxamide 5-amino-4-cyano - 1 and 3-dimethyl-1H-pyrazole 23.10g was added to the mixed liquor of 190ml of concentrated sulfuric acid, and 20ml of water, and it agitated at 90 degrees C for 1.5 hours. The reaction solution was opened in iced water and it neutralized by the sodium hydroxide. The depositing crystal was separated and it dried. Subsequently, this thing was dissolved in the methanol and insoluble matter was filtered, and the solvent was reduced-pressure-distilled off, it dried, and 22.62g of title compounds was obtained.

[0055] 1 H-NMR(DMSO-d6)  $\delta$ ppm; 2.20 (3H, s), 3.43 (3H, s), 6.13 (2H, bs), 6.46 (2H, bs).

[0056] An example 11, 3-dimethyl-5-(5-nitro-2-propoxy benzamide)-1H-pyrazole-4-carboxamide 5-amino - 1 Three - 5-nitro-2-propoxy benzoyl chloride 5.84g (1.2Eq) was dropped at the dimethyl-1H-pyrazole-4-carboxamide 3.08g pyridine 30ml solution, and it agitated at the room temperature for 20 hours. The reaction solution was opened in water, chloroform extracted, and it washed and dried with dilute hydrochloric acid. The silica gel column chromatography

[elution solvent; ethyl-acetate-chloroform (1:2)] refined the residue obtained by carrying out reduced pressure distilling off of the solvent, and 2.30g of title compounds was obtained.

[0057] m.p. 186–188 degree–C1 H-NMR(CDCI3)  $\delta$ tppm; 1.09 (3H, t, J= 7Hz), 2.09 (2H, sext, J= 7Hz) 2.47 (3H, s), 3.79 (3H, s), 4.35 (2H, t, J= 7Hz), 5.60 (2H, bs), 7.16 (1H, d, J= 8Hz), 8.39 (1H, dd, J = 2 or 8Hz), 9.13 (1H, d, J= 2Hz), 11.68 (1H, s).

[0058] An example 24, 5-dihydro – 30ml solution of water of 1.41g of potassium hydroxides (3.0Eq) was added to 1, the 3-dimethyl-6-(5-nitro-2-propoxy phenyl)-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON 1, and a 3-dimethyl-5-(5-nitro-2-propoxy benzamide)-1H-pyrazole-4-carboxamide 3.03g methanol 30ml solution, and it flowed back for 14 hours. The reaction solution was opened in water, it was made hydrochloric-acid acidity, and chloroform extracted. The organic layer was dried after washing in the saturation sodium-hydrogencarbonate water solution, and reduced pressure distilling off of the solvent was carried out. The silica gel column chromatography (elution solvent; 20% ethyl-acetate-chloroform) refined the residue, and 1.53g of title compounds was obtained.

[0059] m.p. 230–232 degree–C1 H-NMR(CDCI3)  $\delta$ tppm; 1.20 (3H, t, J= 7Hz), 2.08 (2H, sext, J= 7Hz) 2.62 (3H, s), 4.03 (3H, s), 4.33 (2H, t, J= 7Hz), 7.19 (1H, d, J= 8Hz), 8.39 (1H, dd, J = 2 or 8Hz), 9.39 (1H, d, J= 2Hz), 10.72 (1H, bs).

[0060] Example 36– (5-amino-2-propoxy phenyl) –4, 5-dihydro – It is 4 and 5-dihydro to the methanol 10ml solution of 1 and 1.00g of 3-dimethyl-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON nickel chlorides (2.0Eq). – 1, 3-dimethyl-6– The (5-nitro-2-propoxy phenyl)-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON 0.72g tetrahydrofuran 20ml solution was added, and 0.31g (4.0Eq) of sodium borohydrides was added little by little under ice-cooling. After agitating a reaction solution for 1 hour, reduced pressure distilling off of the solvent was carried out. The heating dissolution of the residue was carried out at dilute hydrochloric acid, subsequently aqueous ammonia was added, and pH of a solution was adjusted to 8.0. It extracted and dried under chloroform, reduced pressure distilling off of the solvent was carried out, and 0.57g of title compounds was obtained. This thing was used for the next reaction, without refining.

[0061] 7.86 (1H, d, J= 3Hz) 1 H-NMR(CDCI3)  $\delta$ tppm; 1.20 (3H, t, J= 7Hz), 1.97 (3H, t, J= 7Hz), 2.60 (3H, s), 3.97 (3H, s), 4.10 (2H, t, J= 7Hz), 6.8–7.0 (2H, m), 11.21 (1H, bs).

[0062] An example 44, 5-dihydro – 1, 3-dimethyl-6-[5- (Phenoxycarbonylamino) –2-propoxy phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON 6-(5-amino-2-propoxy phenyl)-4, 5-dihydro – 1 3-dimethyl-1H-pyrazolo [3, Triethylamine 0.23g (1.5Eq) was added to 4-d] pyrimidine-4-ON 0.48g 20ml solution of methylene chlorides, and bottom chloro formic acid phenyl of ice-cooling 0.36g (1.5Eq) dropping was carried out. After agitating a reaction solution at a room temperature for 3 hours, it opened in water and chloroform extracted. Carried out reduced pressure distilling off of the solvent after desiccation, it was made to crystallize by the ethyl-acetate-hexane, and 0.51g of title compounds was obtained. This thing was used for the next reaction, without refining.

[0063] 1 H-NMR(CDCI3)  $\delta$ tppm; 1.17 (3H, t, J= 7Hz), 2.01 (2H, sext, J= 7Hz) 2.61 (3H, s), 3.98 (3H, s), 4.19 (2H, t, J= 7Hz), 7.0–7.5 (7H, m), 7.83 (1H, dd, J = 3 or 9Hz), 8.44 (1H, d, J= 3Hz), 11.10 (1H, s).

[0064] An example 54, 5-dihydro – 1, 3-dimethyl-6-[5- The (morpholino carbonylamino)-2-propoxy phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON 4, 5-dihydro – 1 3-dimethyl-6-[5-(phenoxycarbonylamino)-2-propoxy phenyl]-1H-pyrazolo [3, 20ml solution (4-d] pyrimidine-4-ON 300mg and morpholine 185mg (3.0Eq)) of N,N-dimethylformamide was agitated at 80 degrees C for 3 hours. The reaction solution was opened in water and ethyl acetate extracted. After desiccation, reduced pressure distilling off of the solvent was carried out, the silica gel column chromatography (elution solvent; ethyl acetate) refined the residue, and 267mg of title compounds was obtained.

[0065] m.p. 244–246 degree–C1 H-NMR(CDCI3)  $\delta$ tppm; 1.12 (3H, t, J= 7Hz), 1.93 (2H, sext, J= 7Hz) 2.59 (3H, s), 3.56 (4H, t, J= 5Hz) 3.78 (4H, t, J= 5Hz), 3.91 (3H, s), 4.12 (2H, t, J= 7Hz), 6.82 (1H, s), 7.00 (1H, d, J= 9Hz), 7.81 (1H, dd, J = 3 or 9Hz), 8.17 (1H, d, J= 3Hz), 11.09 (1H, bs).

[0066] An example 64, 5-dihydro – It is made to be the same as that of 1 and the 3-dimethyl-6-[5-(piperidino carbonylamino)-2-propoxy phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON

example 5. 4, 5-dihydro - The title compound was obtained from 1, 3-dimethyl-6-[5-(phenoxycarbonylamino)-2-propoxy phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON, and a piperidine.

[0067] m.p. 232-234 degree-C<sup>1</sup> H-NMR(CDCl<sub>3</sub>)  $\delta$ ppm; 1.14 (3H, t, J= 7Hz), 1.6- 1.8 (6H, m) and 1.96 (2H, sext, J= 7Hz) -- 2.60 (3H, s) and 3.4- 3.6 (4H, m) and 3.93 (3H, s) -- 4.13 (2H, t, J= 7Hz), 6.58 (1H, s), 6.98 (1H, d, J= 9Hz), 7.79 (1H, dd, J = 3 or 9Hz), 8.15 (1H, d, J= 3Hz), 11.07 (1H, s).

[0068] an example -- 76 - [ -- five - [(4-cull BETOKISHI piperidino) -- carbonylamino --] - two - propoxy one -- phenyl --] - four -- five - dihydro one - one -- three - dimethyl - one -- H - pyrazolo -- [ -- three -- four - d --] -- a pyrimidine - four - ON -- an example -- five -- the same -- carrying out -- 4, 5-dihydro - The title compound was obtained from 1, and 3-dimethyl-6-[5-(phenoxycarbonylamino)-2-propoxy phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON and isonipecotic acid ethyl.

[0069] m.p. 205-207 degree-C<sup>1</sup> H-NMR(CDCl<sub>3</sub>)  $\delta$ ppm; 1.13 (3H, t, J= 7Hz), 1.27 (3H, t, J= 7Hz), 1.7-2.1 (6H, m), 2.4-2.6 (1H, m), 2.59 (3H, s), 3.0-3.2 (2H, m), 3.88 (3H, s), 4.0-4.2 (6H, m), 6.74 (1H, s), 6.97 (1H, d, J= 9Hz), 7.76 (1H, dd, J = 3 or 9Hz), 8.12 (1H, d, J= 3Hz), 11.02 (1H, bs).

[0070] The title compound was obtained from the 4-amino -1 and 3-dimethyl-1H-pyrazole-4-carboxamide and 2-ethoxy-5-nitrobenzoyl chloride like the example 81 and the 3-dimethyl-5-(2-ethoxy-5-nitro benzamide)-1H-pyrazole-4-carboxamide example 1.

[0071] m.p. 191-193 degree-C<sup>1</sup> H-NMR(DMSO-d<sub>6</sub>)  $\delta$ ppm; 1.44 (3H, t, J= 7Hz), 2.30 (3H, s), 3.63 (3H, s), 4.39 (2H, q, J= 7Hz), 6.70 (1H, bs), 7.20 (1H, bs), 7.45 (1H, d, J= 8Hz), 8.42 (1H, dd, J = 2 or 8Hz), 8.56 (1H, d, J= 2Hz), 10.44 (1H, s).

[0072] An example 94, 5-dihydro - The title compound was obtained from 1 and the 3-dimethyl-5-(2-ethoxy-5-nitro benzamide)-1H-pyrazole-4-carboxamide like 1 and the 3-dimethyl-6-(2-ethoxy-5-nitrophenyl)-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON example 2.

[0073] m.p. 266-268 degree-C<sup>1</sup> H-NMR(CDCl<sub>3</sub>)  $\delta$ ppm; 1.67 (3H, t, J= 7Hz), 2.61 (3H, s), 4.03 (3H, s), 4.45 (2H, q, J= 7Hz), 7.18 (1H, d, J= 8Hz), 8.39 (1H, dd, J = 2 or 8Hz), 9.38 (1H, d, J= 2Hz), 10.71 (1H, bs).

[0074] Example 106-(5-amino-2-ethoxy phenyl)-4, 5-dihydro - It is 4 and 5-dihydro like 1 and the 3-dimethyl-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON example 3. - The title compound was obtained from 1 and 3-dimethyl-6-(2-ethoxy-5-nitrophenyl)-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON.

[0075] 7.84 (1H, d, J= 2Hz) 1 H-NMR(CDCl<sub>3</sub>)  $\delta$ ppm; 1.54 (3H, t, J= 7Hz), 2.60 (3H, s), 3.66 (2H, bs), 3.96 (3H, s), 4.20 (2H, q, J= 7Hz), 6.8-7.0 (2H, m), 11.20 (1H, bs).

[0076] an example 114 and 5-dihydro -1 and the 3-dimethyl-6-[2-ethoxy-5-(phenoxycarbonylamino) phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON example 4 -- the same -- carrying out -- 6-(5-amino-2-ethoxy phenyl)-4, 5-dihydro - 1 Three - The title compound was obtained from dimethyl-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON and chloro formic acid phenyl.

[0077] 1 H-NMR(CDCl<sub>3</sub>)  $\delta$ ppm; 1.59 (3H, t, J= 7Hz), 2.61 (3H, s), 3.98 (3H, s), 4.30 (2H, q, J= 7Hz), 7.0-7.5 (7H, m), 7.83 (1H, dd, J = 2 or 8Hz), 8.43 (1H, d, J= 2Hz), 11.07 (1H, s).

[0078] an example 124 and 5-dihydro -1 and the 3-dimethyl-6-[2-ethoxy-5-(morpholino carbonylamino) phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON example 5 -- the same -- carrying out -- 4, 5-dihydro-1, and 3-dimethyl-6- the title compound was obtained from [2-ethoxy-5-(phenoxycarbonylamino) phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON and a morpholine.

[0079] m.p. 243-245 degree-C<sup>1</sup> H-NMR(CDCl<sub>3</sub>)  $\delta$ ppm; 1.55 (3H, t, J= 7Hz), 2.61 (3H, s), 3.55 (4H, t, J= 5Hz), 3.78 (4H, t, J= 5Hz), 3.95 (3H, s), 4.26 (2H, q, J= 7Hz), 6.70 (1H, s), 7.01 (1H, d, J= 9Hz), 7.81 (1H, dd, J = 3 or 9Hz), 8.21 (1H, d, J= 3Hz), 11.11 (1H, bs).

[0080] an example 134 and 5-dihydro -1 and the 3-dimethyl-6-[2-ethoxy-5-(piperidino carbonylamino) phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON example 5 -- the same -- carrying out -- 4, 5-dihydro-1, and 3-dimethyl-6- the title compound was obtained from [2-ethoxy-5-(phenoxycarbonylamino) phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON and a piperidine.

[0081] m.p. 227-230 degree-C1 H-NMR(CDCl<sub>3</sub>)  $\delta$ tppm; 1.57 (3H, t, J= 7Hz), 1.6-1.8 (6H, m), 2.59 (3H, s), 3.4-3.6 (4H, m), 3.95 (3H, s), 4.25 (2H, q, J= 7Hz), 6.50 (1H, bs), 6.99 (1H, d, J= 9Hz), 7.80 (1H, dd, J = 3 or 9Hz), 8.16 (1H, d, J= 3Hz), 11.03 (1H, bs).

[0082] an example -- 146 - [-- five - [(4-cull BETOKISHI piperidino) -- carbonylamino --] - two - ethoxy -- phenyl --] - four -- five - dihydro one - one -- three - dimethyl - one -- H - pyrazolo -- [-- three -- four - d --] -- a pyrimidine - four - ON -- an example -- five -- the same -- carrying out -- 4, 5-dihydro-1, and 3-dimethyl-6- the title compound was obtained from [2-ethoxy-5-(phenoxycarbonylamino) phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON and isonipecotic acid ethyl.

[0083] m.p. 124-127 degree-C1 H-NMR(CDCl<sub>3</sub>)  $\delta$ tppm; 1.27 (3H, t, J= 7Hz), 1.57 (3H, t, J= 7Hz), 1.8-2.1 (4H, m), 2.5-2.7 (1H, m), 2.59 (3H, s), 3.0-3.2 (2H, m), 3.95 (3H, s) and 4.0- 4.1 (2H, m) and 4.16 (2H, q, J= 7Hz) -- 4.26 (2H, q, J= 7Hz), 6.51 (1H, s), 7.01 (1H, d, J= 9Hz), 7.77 (1H, dd, J = 3 or 9Hz), 8.17 (1H, d, J= 3Hz), 11.05 (1H, bs).

[0084] an example 154 and 5-dihydro -1 and the 3-dimethyl-6-[2-ethoxy-5-(pyrrolidino carbonylamino) phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON example 5 -- the same -- carrying out -- 4, 5-dihydro-1, and 3-dimethyl-6- the title compound was obtained from [2-ethoxy-5-(phenoxycarbonylamino) phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON and a pyrrolidine.

[0085] m.p. 258-263 degree-C1 H-NMR(CDCl<sub>3</sub>)  $\delta$ tppm; 1.53 (3H, t, J= 7Hz), 1.9-2.1 (4H, m), 2.60 (3H, s), 3.4-3.6 (4H, m), 3.96 (3H, s), 4.26 (2H, q, J= 7Hz), 6.28 (1H, bs), 7.01 (1H, d, J= 9Hz), 7.88 (1H, dd, J = 3 or 9Hz), 8.20 (1H, d, J= 3Hz), 11.08 (1H, bs).

[0086] an example -- 166 - [-- five - [-- [-- a screw (2-hydroxyethyl) -- amino --] -- carbonylamino --] - two - ethoxy -- phenyl --] - four -- five - dihydro ones - one -- three - dimethyl - one -- H - pyrazolo -- [-- three -- four - d --] -- a pyrimidine - four - ON -- an example -- five -- the same -- carrying out -- 4, 5-dihydro-1, and 3-dimethyl-6- the title compound was obtained from [2-ethoxy-5-(phenoxycarbonylamino) phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON and diethanolamine.

[0087] m.p. 210-212 degree-C1 H-NMR(DMSO-d<sub>6</sub>)  $\delta$ tppm; 1.32 (3H, t, J= 7Hz), 2.43 (3H, s) and 3.4- 3.7 (8H, m) and 3.83 (3H, s) -- 4.12 (2H, q, J= 7Hz), 5.02 (2H, m), 7.08 (1H, d, J= 9Hz), 7.53 (1H, dd, J = 3 or 9Hz), 7.78 (1H, d, J= 3Hz), 8.62 (1H, s), 11.73 (1H, bs).

[0088] an example -- 174 -- five - dihydro one - six - [-- five - [-- [(1, 3-dihydroxy propyl) -- amino --] -- carbonylamino --] - two - ethoxy -- phenyl --] - one -- three - dimethyl - one - - H - pyrazolo -- [-- three -- four - d --] -- a pyrimidine - four - ON -- an example -- five -- the same -- carrying out -- 4, 5-dihydro-1, and 3-dimethyl-6- the title compound was obtained from [2-ethoxy-5-(phenoxycarbonylamino) phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON and 2-amino-1,3-propanediol.

[0089] m.p. 260-265 degree-C1 H-NMR(DMSO-d<sub>6</sub>)  $\delta$ tppm; 1.32 (3H, t, J= 7Hz), 2.44 (3H, s) and 3.3- 3.7 (5H, m) and 3.83 (3H, s) -- 4.12 (2H, q, J= 7Hz) 4.72 (2H, t, J= 5Hz), 5.98 (1H, d, J= 8Hz), 7.08 (1H, d, J= 9Hz), 7.52 (1H, dd, J = 3 or 9Hz), 7.84 (1H, d, J= 3Hz), 8.66 (1H, s), 11.69 (1H, bs).

[0090] an example -- 184 -- five - dihydro one - one -- three - dimethyl - six - [-- two - ethoxy - five - [(4-hydroxy piperidino) -- carbonylamino --] -- phenyl --] - one -- H - pyrazolo -- [-- three -- four - d --] -- a pyrimidine - four - ON -- an example -- five -- the same -- carrying out -- 4, 5-dihydro-1, and 3-dimethyl-6- the title compound was obtained from [2-ethoxy-5-(phenoxycarbonylamino) phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON and a 4-hydroxy piperidine.

[0091] m.p. 230-232 degree-C1 H-NMR(CDCl<sub>3</sub>)  $\delta$ tppm; 1.57 (3H, t, J= 7Hz), 1.6-1.7 (2H, m), and 1.9- 2.1 (2H, m) and 2.59 (3H, s) -- 3.2-3.2 (2H, m), and 3.8- 4.1 (3H, m) and 3.94 (3H, s) -- 4.26 (2H, q, J= 7Hz), 6.57 (1H, s), 7.01 (1H, d, J= 9Hz), 7.78 (1H, dd, J = 3 or 9Hz), 8.17 (1H, d, J= 3Hz), 11.06 (1H, bs).

[0092] an example -- 194 -- five - dihydro one - one -- three - dimethyl - six - [-- two - ethoxy - five - [(4-methyl piperazino) -- carbonylamino --] -- phenyl --] - one -- H - pyrazolo -- [-- three -- four - d --] -- a pyrimidine - four - ON -- an example -- five -- the same -- carrying out -- 4, 5-dihydro-1, and 3-dimethyl-6- the title compound was obtained from [2-

ethoxy-5-(phenoxy-carbonylamino) phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON and N-methyl piperazine.

[0093] m.p. 185-190 degree-C1 H-NMR(CDCl<sub>3</sub>)  $\delta$ ppm; 1.53 (3H, t, J= 7Hz), 2.37 (3H, s), 2.50 (2H, m), 2.58 (3H, s), 3.58 (2H, m), 3.88 (3H, s), 4.21 (2H, q, J= 7Hz), 6.76 (1H, s), 6.96 (1H, d, J= 9Hz), 7.77 (1H, dd, J = 3 or 9Hz), 8.12 (1H, d, J= 3Hz), 11.00 (1H, bs).

[0094] an example 204 and 5-dihydro -1 and the 3-dimethyl-6-[2-propoxy-5-(thiomorpholino carbonyl amino) phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON example 5 -- the same -- carrying out -- 4, 5-dihydro - The title compound was obtained from 1, and 3-dimethyl-6-[5-(phenoxy-carbonylamino)-2-propoxy phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON and a thio morpholine.

[0095] m.p. 249-252 degree-C1 H-NMR(CDCl<sub>3</sub>)  $\delta$ ppm; 1.13 (3H, t, J= 7Hz), 1.95 (2H, sext, J= 7Hz) 2.59 (3H, s), 2.6-2.8 (4H, m), and 3.8- 3.9 (4H, m) and 3.88 (3H, s) -- 4.11 (2H, t, J= 7Hz), 6.70 (1H, s), 6.98 (1H, d, J= 9Hz), 7.76 (1H, dd, J = 3 or 9Hz), 8.12 (1H, d, J= 3Hz), 11.00 (1H, s).

[0096] an example 214 and 5-dihydro -1 and the 3-dimethyl-6-[2-ethoxy-5-(thia ZORIJINO carbonylamino) phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON example 5 -- the same -- carrying out -- 4, 5-dihydro-1, and 3-dimethyl-6- the title compound was obtained from [2-ethoxy-5-(phenoxy-carbonylamino) phenyl]-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON and thiazolidine.

[0097] m.p. 216-218 degree-C1 H-NMR(CDCl<sub>3</sub>)  $\delta$ ppm; 1.56 (3H, t, J= 7Hz), 2.59 (3H, s), 3.14 (2H, t, J= 6Hz), 3.85 (2H, t, J= 6Hz), 3.91 (3H, s), 4.24 (2H, s), 4.62 (2H, s), 6.57 (1H, s), 7.00 (1H, d, J= 9Hz), 7.81 (1H, dd, J = 3 or 9Hz), 8.19 (1H, d, J= 3Hz), 11.01 (1H, bs).

[0098] An example 224, 5-dihydro - 1, 3-dimethyl-6- (2-ethoxy-5-ureido phenyl)-1H-pyrazolo [3, 4-d] pyrimidine-4-ON 6- (5-amino-2-propoxy phenyl) -4, 5-dihydro - 5ml solution of water of 520mg of potassium cyanate (5.0Eq) was added to 10ml solution of 1 and 3-dimethyl-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON 400mg acetic acids, and it agitated at the room temperature for 3 hours. The depositing crystal was separated and it washed with water. Reduced pressure drying of the obtained crystal was carried out, and 410mg of title compounds was obtained.

[0099] 1 H-NMR(DMSO-d<sub>6</sub>)  $\delta$ ppm; 0.96 (3H, t, J= 7Hz), 1.73 (2H, sext, J= 7Hz) 2.44 (3H, s), 3.84 (3H, s), 4.01 (2H, t, J= 7Hz), 5.80 (2H, s), 7.09 (1H, d, J= 9Hz), 7.59 (1H, dd, J = 3 or 9Hz), 7.84 (1H, d, J= 3Hz), 8.58 (1H, s), 11.64 (1H, bs).

[0100] Example 236-[5-[ (4-carboxy piperidino) Carbonylamino]-2-ethoxy phenyl] -4, 5-dihydro - 1, 3-dimethyl-1H-[3 and 4-pyrazolo d] pyrimidine-4-ON 6-[5-[ (4-cull BETOKISHI piperidino) carbonylamino]-2-ethoxy phenyl]-4, 5-dihydro - 1 3-dimethyl-1H-pyrazolo [3, 2ml solution of water of 0.18g of potassium carbonate was added to the 4-d] pyrimidine-4-ON 0.20g methanol 10ml solution, and it agitated at the room temperature overnight. After adding the hydrochloric acid to the reaction solution 10%, being referred to as pH1 and filtration and water washing the depositing crystal, reduced pressure drying was carried out and 0.15g of title compounds was obtained.

[0101] m.p. 232-234 degree-C1 H-NMR(DMSO-d<sub>6</sub>)  $\delta$ ppm; 1.32 (3H, t, J= 7Hz), 1.4-1.6 (2H, m), 1.8-1.9 (2H, m), 2.4-2.6 (1H, m), 2.43 (3H, s) and 2.8- 3.0 (2H, m) and 3.84 (3H, s) -- 3.9-4.1 (2H, m), 4.11 (2H, q, J= 7Hz), 7.09 (1H, d, J= 9Hz), 7.61 (1H, dd, J = 3 or 9Hz), 7.86 (1H, d, J= 3Hz), 8.54 (1H, s), 11.70 (1H, bs).

[0102] The example of a trial (phosphodiesterase inhibitory action)

The FRLC system which used MonoQHR5/5 column from the dog main artery meltable fraction refined the phosphodiesterase isozyme. namely, -- extraction -- an organization -- 25 -- mM -- tris -- a hydrochloric acid -- the buffer solution -- 250 -- mM -- scrolling -- two -- mM -- a magnesium chloride -- one -- mM -- ethylene glycol -- a screw (beta-aminoethyl ether) -- N -- N -- N -- ' -- N -- ' -- four -- an acetic acid -- one -- mM -- dithiothreitol -- and -- various kinds -- protease inhibitor -- existence -- the bottom -- having homogenized -- after -- a salt -- inclination -- protein -- a fraction -- elution -- carrying out -- each -- a fraction -- phosphodiesterase -- activity -- measuring -- things -- the mixed fraction of calcium calmodulin dependency phosphodiesterase and cyclic GMP specific phosphodiesterase -- having obtained . Furthermore, separation purification of both was carried out with the calmodulin ANAFINI tea chromatography.

[0103] the approach by which measurement of phosphodiesterase activity was indicated by . Biochem.Biophys.Res.Comm., the 148th volume, and the 1468th page (1987, S.Matsushima et al.) -- following -- dog main artery cyclic GMP specific phosphodiesterase -- as an active factor -- the 0.2mM ethylene glycol screws (beta-aminoethyl ether) N and N, N', and N' -- 0.4mM [3H] cyclic GMP was measured as a substrate under -4 acetic-acid existence.

[0104] The test drug was used as a dimethyl sulfoxide solution 10% after dissolving in dimethyl sulfoxide 100%. The last concentration under reaction was used as dimethyl sulfoxide 1%.

[0105] A result is shown in Table 4.

[0106]

[Table 4]

検 体	I C <sub>50</sub> 値 ( n M )
5	2. 4
6	1. 5
7	6. 0
1 2	3. 4
1 3	6. 7
1 4	9. 9
1 5	1 4
1 6	2 2
1 8	8. 5
1 9	2 4
2 0	9. 3
2 1	1 1
2 2	2 9

[Translation done.]

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	A B N			A B N
	A B S			A B S
	A B U			A B U

審査請求 未請求 請求項の数 2 O L (全 13 頁) 最終頁に続く

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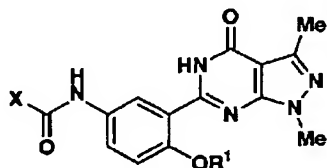
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(54) 【発明の名称】 1H-ピラゾロ [3, 4-d] ピリミジン-4-オン誘導体

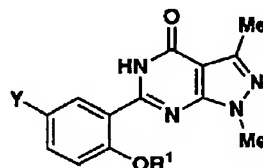
(57) 【要約】 (修正有)

【目的】 新しいタイプのサイクリックGMP特異的ホスホジエステラーゼ阻害作用を有する化合物を提供し、高血圧症、狭心症、心不全、心筋梗塞、動脈硬化症、喘息、気管支炎のごとき慢性可逆閉塞性肺炎、アトピー性皮膚炎およびアレルギー性鼻炎などの治療に役立てる。

【構成】



〔式中、R¹は炭素原子数1～4個のアルキル基、Xはフェノキシ基またはR²R³N基、R²、R³は同一もしくは異なって水素原子または炭素原子数2～4個のヒドロキシアルキル基を示すか、またはR²R³N基としてモルホリノ基、ピペリジノ基など、を示す。〕で表わされる1H-ピラゾロ [3, 4-d] ピリミジン-4-オン誘導体およびその塩。



〔式中、R¹は炭素原子数1～4個のアルキル基、Yはアミノ基またはニトロ基を示す。〕で表わされる1H-ピラゾロ [3, 4-d] ピリミジン-4-オン誘導体およびその塩。

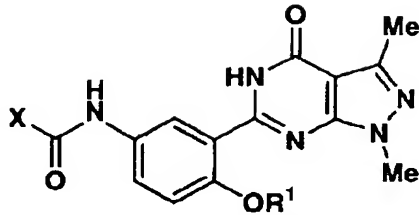


1

【特許請求の範囲】

【請求項 1】

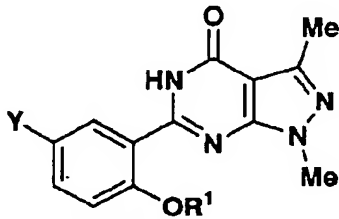
【化 1】



【化 1 中、R¹は炭素原子数 1～4 個のアルキル基を示し、X はフェノキシ基または R²R³N 基を示す。ここで R²、R³は同一もしくは異なって水素原子または炭素原子数 2～4 個のヒドロキシアルキル基を示すか、または R²R³N 基としてモルホリノ基、ピペリジノ基、ピロリジノ基、4-ヒドロキシピペリジノ基、4-カルベトキシピペリジノ基、4-カルボキシピペリジノ基、チオモルホリノ基、チアゾリノ基または 4-メチルピペラジノ基を示す。】で表わされる 1H-ピラゾロ [3, 4-d] ピリミジン-4-オン誘導体およびその塩。

【請求項 2】

【化 2】



【化 2 中、R¹は炭素原子数 1～4 個のアルキル基を示し、Y はアミノ基またはニトロ基を示す。】で表わされる 1H-ピラゾロ [3, 4-d] ピリミジン-4-オン誘導体およびその塩。

【発明の詳細な説明】

【0001】

【産業上の利用分野】本発明は、サイクリック GMP 特異的ホスホジエステラーゼ阻害作用を有する 1H-ピラゾロ [3, 4-d] ピリミジン-4-オン誘導体に関する。

【0002】

【従来の技術】従来、1H-ピラゾロ [3, 4-d] ピリミジン骨格を有するサイクリック GMP 特異的ホスホジエステラーゼ阻害剤としては EP 349239 号の化合物が知られている。また、WO 93/07149 号では、2 位のフェニル基の 5 位に置換基を導入することで強いサイクリック GMP 特異的ホスホジエステラーゼ阻害作用を有する化合物を報告しているが、本発明で示すウレイド基を置換基として持つ化合物の記載はない。

【0003】

【発明が解決しようとする課題】本発明の目的は、強い

2

サイクリック GMP 特異的ホスホジエステラーゼ阻害作用を有する化合物を提供し、ひいては高血圧症、狭心症、心不全、心筋梗塞、動脈硬化症、喘息、気管支炎のごとき慢性可逆閉塞性肺炎、アトピー性皮膚炎およびアレルギー性鼻炎などの治療に役立てることにある。

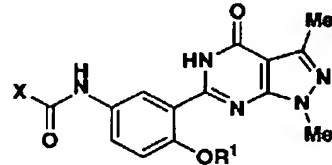
【0004】

【課題を解決するための手段】本発明者らは、サイクリック GMP 特異的ホスホジエステラーゼ阻害作用を有する化合物を鋭意検討した結果、ある種の 1H-ピラゾロ [3, 4-d] ピリミジン-4-オン骨格を有する化合物が当該目的を満たすことを見だし、さらにその知見に基づき本発明を完成した。

【0005】すなわち本発明は、

【0006】

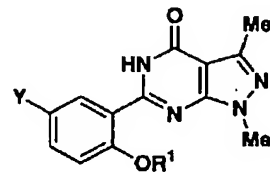
【化 3】



【0007】【化 3 中、R¹は炭素原子数 1～4 個のアルキル基を示し、X はフェノキシ基または R²R³N 基を示す。ここで R²、R³は同一もしくは異なって水素原子または炭素原子数 2～4 個のヒドロキシアルキル基を示すか、または R²R³N 基としてモルホリノ基、ピペリジノ基、ピロリジノ基、4-ヒドロキシピペリジノ基、4-カルベトキシピペリジノ基、4-カルボキシピペリジノ基、チオモルホリノ基、チアゾリノ基または 4-メチルピペラジノ基を示す。】で表わされる 1H-ピラゾロ [3, 4-d] ピリミジン-4-オン誘導体およびその塩および

【0008】

【化 4】



【0009】【化 4 中、R¹は炭素原子数 1～4 個のアルキル基を示し、Y はアミノ基またはニトロ基を示す。】で表わされる 1H-ピラゾロ [3, 4-d] ピリミジン-4-オン誘導体およびその塩である。

【0010】本発明において炭素原子数 1～4 個のアルキル基とは、メチル基、エチル基、プロピル基、イソプロピル基などの直鎖状または分枝鎖状のアルキル基をいう。炭素原子数 2～4 個のヒドロキシアルキル基とは、2-ヒドロキシエチル基、3-ヒドロキシプロピル基、2-ヒドロキシ-2-メチルプロピル基、4-ヒドロキ

3

4

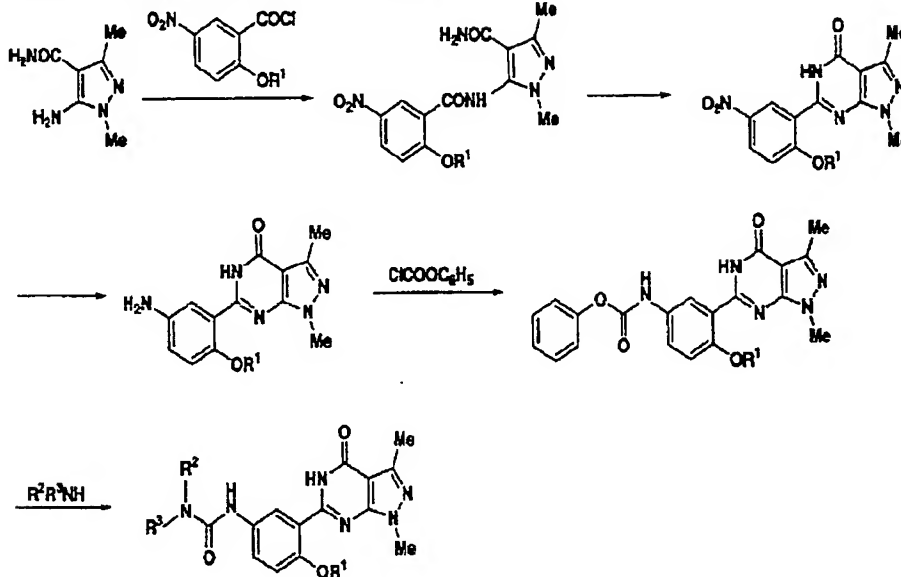
シブチル基、2, 3-ジヒドロキシプロピル基、1, 3-ジヒドロキシ-2-プロピル基などの直鎖状または分枝鎖状のモノまたはジヒドロキシアルキル基をいう。

【0011】本発明の化合物は、例えば化5に示す製造\*

\*スキームにより製造することができる。

【0012】

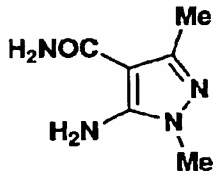
【化5】



【0013】【化5中、R<sup>1</sup>、R<sup>2</sup>およびR<sup>3</sup>、は前記と同意義である。】出発原料である化6で表わされる5-アミノ-1H-ピラゾール-4-カルボキサミド

【0014】

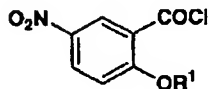
【化6】



【0015】と

【0016】

【化7】

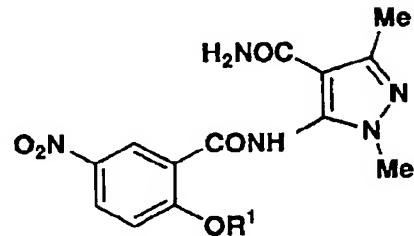


【0017】【化7中、R<sup>1</sup>は前記と同意義である。】

で表わされる化合物を塩基存在下反応させ、

【0018】

【化8】



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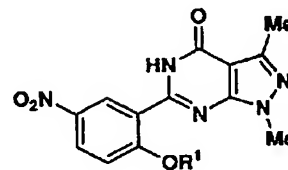
【0019】【化8中、R<sup>1</sup>は前記と同意義である。】で表わされる化合物を得る。

【0020】ここで、塩基としてはトリエチルアミン、ピリジン等の有機塩基を用いることができ、反応溶媒としてはN, N-ジメチルホルムアミド、テトラヒドロフラン、アセトン、クロロホルム、ジクロロメタン等の溶媒を単独または混合して用いることができる。反応温度は0℃から還流温度である。

40 【0021】【化8で表わされる化合物を塩基で処理することにより、

【0022】

【化9】

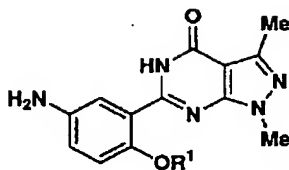


50 【0023】【化9中、R<sup>1</sup>は前記と同意義である。】

で表わされる化合物を得、化9のニトロ基を還元することにより

【0024】

【化10】



【0025】【化10中、R<sup>1</sup>は前記と同意義である。】で表わされる化合物を得る。

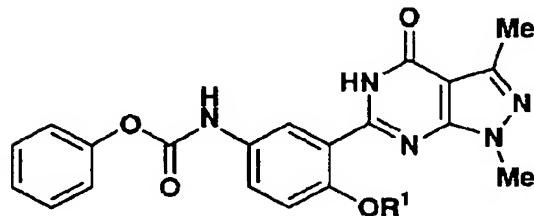
【0026】ここで、用いる塩基としては水酸化カリウム、水酸化ナトリウム等の無機塩基を用いることができ、反応溶媒としてはメタノール、エタノール等のアルコール系溶媒を用いることができ、また、過酸化水素水を添加することができる。反応温度は室温から還流温度である。

【0027】また、還元剤としてはパラジウム炭素-水素、塩化ニッケル-水素化ホウ素ナトリウム、鉄-酢酸等の還元剤を用いることができ、反応溶媒としてはメタノール、エタノール、テトラヒドロフラン、酢酸等の溶媒を単独または混合して用いることができる。反応温度は0℃から還流温度である。

【0028】ついで、化10で表わされる化合物に塩基存在下、クロロギ酸フェニルを反応させ、

【0029】

【化11】



【0030】【化11中、R<sup>1</sup>は前記と同意義である。】で表わされる化合物を得る。

【0031】ここで、用いる塩基としてはトリエチルアミン、ピリジン等の有機塩基を用いることができ、反応溶媒としてはN,N-ジメチルホルムアミド、テトラヒドロフラン、アセトン等の溶媒を用いることができる。反応温度は室温から還流温度である。

【0032】ついで、化11で表わされる化合物と1~\*

\*5当量の式(1)

R<sup>2</sup>R<sup>3</sup>NH

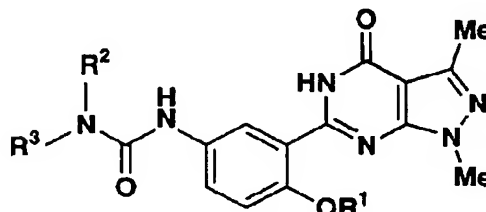
(1)

【式1中、R<sup>2</sup>およびR<sup>3</sup>は前記と同意義である。】で表わされるアミンを反応させることにより

【0033】

【化12】

10



【0034】【化12中、R<sup>1</sup>、R<sup>2</sup>およびR<sup>3</sup>は前記と同意義である。】で表わされる化合物を得ることができる。

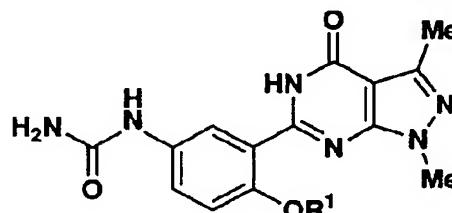
【0035】ここで、反応溶媒としてはN,N-ジメチルホルムアミド、テトラヒドロフラン、アセトン等の溶媒を用いることができる。反応温度は0℃から還流温度である。

【0036】また、化12においてR<sup>2</sup>およびR<sup>3</sup>が水素原子である

【0037】

【化13】

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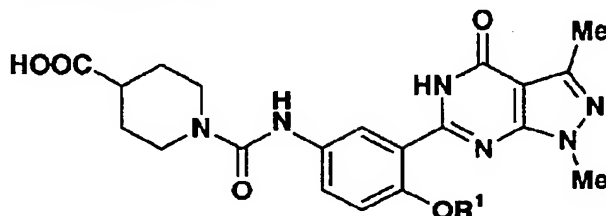
【0038】【化13中、R<sup>1</sup>は前記と同意義である。】で表される化合物は化10で表される化合物と酸存在下、1~5当量のシアン酸カリウムまたはシアン酸ナトリウムを反応させることにより得ることができる。

【0039】ここで、酸としては酢酸等の有機酸を用いることができる。反応溶媒としては水、酢酸等の溶媒を単独または混合して用いることができる。反応温度は0℃から還流温度である。

【0040】また、化12においてR<sup>2</sup>R<sup>3</sup>N基が4-カルボキシピペリジノ基である

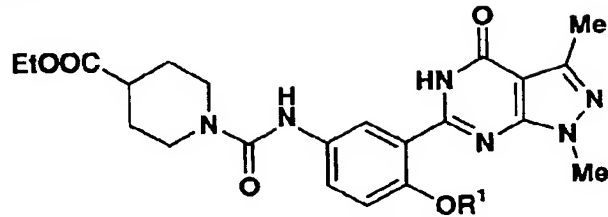
【0041】

【化14】



【0042】【化14中、R<sup>1</sup>は前記と同意義である。】で表される化合物は塩基存在下、

\* 【0043】  
\* 【化15】



【0044】【化15中、R<sup>1</sup>は前記と同意義である。】で表される化合物を加水分解することにより得ることができる。

【0045】ここで、塩基としては炭酸カリウム、水酸化ナトリウム、水酸化カリウム等の無機塩基を用いることができ、反応溶媒としては水、メタノール、エタノール等を用いることができる。反応温度は室温から還流温度である。

【0046】

【発明の効果】本発明の目的は、強いサイクリックGM P特異的ホスホジエステラーゼ阻害作用を有し、ひいて

10 は高血圧症、狭心症、心不全、心筋梗塞、動脈硬化症、喘息、気管支炎のごとき慢性可逆閉塞性肺炎、アトピー性皮膚炎およびアレルギー性鼻炎などの治療に有用である。

【0047】

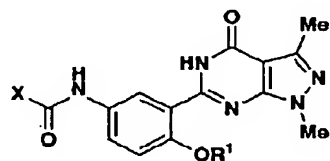
【実施例】以下、参考例および実施例を挙げて本発明を更に詳細に説明する。

【0048】また、実施例1～23により製造した化合物の構造式を表1～3に示す。

【0049】

20 【表1】

構造式



No.	R¹	X
4	Pr	PhO
5	Pr	
6	Pr	
7	Pr	EtOOC-
11	Et	PhO
12	Et	
13	Et	
14	Et	EtOOC-
15	Et	
16	Et	(HOCH₂CH₂)₂N-
17	Et	(HOCH₂)₂CHNH-
18	Et	HO-
19	Et	Me-N-
20	Pr	

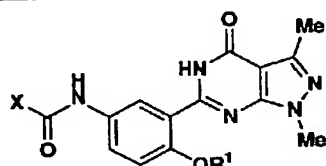
【0050】

【表2】

11

12

構造式

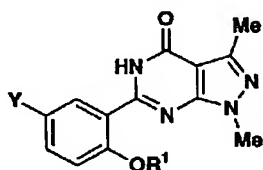


No.	R¹	X
20	Pr	
21	Et	
22	Pr	H₂N-
23	Et	HOOC-

【0051】

\* \* 【表3】

構造式



No.	R¹	Y
2	Pr	O₂N-
3	Pr	H₂N-
9	Et	O₂N-
10	Et	H₂N-

【0052】参考例1

5-アミノ-4-シアノ-1, 3-ジメチル-1H-ピラゾール

(1-エトキシエチリデン) マロニトリル 27.2 g とメチルヒドラジン 9.2 g (1.0当量) のメタノール 300 ml 溶液を 3 時間還流した。反応溶液を一晩放置後、溶媒を減圧留去し、酢酸エチルを加えて結晶を濾取、乾燥して標題化合物 17.84 g を得た。

【0053】¹H-NMR (DMSO-d₆) δ ppm; 2.05 (3H, s), 3.44 (3H, s), 6.44 (2H, bs).

【0054】参考例2

5-アミノ-1, 3-ジメチル-1H-ピラゾール-4-カルボキサミド

5-アミノ-4-シアノ-1, 3-ジメチル-1H-ピラゾール 23.10 g を濃硫酸 190 ml と水 20 ml の混合液に加え、90℃で 1.5 時間攪拌した。反応溶液を氷水にあげ、水酸化ナトリウムで中和した。析出した結晶を濾取し、乾燥した。次いでこのものをメタノールに溶解して不溶物を濾過し、溶媒を減圧留去、乾燥して標題化合物 22.62 g を得た。

【0055】¹H-NMR (DMSO-d₆) δ ppm; 2.20 (3H, s), 3.43 (3H, s), 6.13 (2H, bs), 6.46 (2H, bs).

【0056】実施例1

1, 3-ジメチル-5-(5-ニトロ-2-プロポキシベンズアミド)-1H-ピラゾール-4-カルボキサミド

5-アミノ-1, 3-ジメチル-1H-ピラゾール-4-カルボキサミド 3.08 g のピリジン 30 ml 溶液に 5-ニトロ-2-プロポキシベンゾイルクロライド 5.84 g (1.2当量) を滴下し、室温で 20 時間攪拌した。反応溶液を水にあげ、クロロホルムで抽出し、希塩酸で洗浄して乾燥した。溶媒を減圧留去して得られた残留物をシリカゲルカラムクロマトグラフィー [溶出溶媒: 酢酸エチル-クロロホルム (1:2)] で精製して標題化合物 2.30 g を得た。

【0057】m. p. 186~188℃

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  ppm; 1.09 (3H, t,  $J=7\text{Hz}$ ), 2.09 (2H, sext,  $J=7\text{Hz}$ ), 2.47 (3H, s), 3.79 (3H, s), 4.35 (2H, t,  $J=7\text{Hz}$ ), 5.60 (2H, bs), 7.16 (1H, d,  $J=8\text{Hz}$ ), 8.39 (1H, dd,  $J=2, 8\text{Hz}$ ), 9.13 (1H, d,  $J=2\text{Hz}$ ), 11.68 (1H, s).

#### 【0058】実施例2

4, 5-ジヒドロ-1, 3-ジメチル-6-(5-ニトロ-2-プロポキシフェニル)-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン 10  
1, 3-ジメチル-5-(5-ニトロ-2-プロポキシベンズアミド)-1H-ピラゾール-4-カルボキサミド 3.03gのメタノール30ml溶液に水酸化カリウム1.41g (3.0当量)の水30ml溶液を加え、14時間還流した。反応溶液を水にあげ、塩酸酸性にしてクロロホルムで抽出した。有機層を飽和炭酸水素ナトリウム水溶液で洗浄後、乾燥して溶媒を減圧留去した。残留物をシリカゲルカラムクロマトグラフィー(溶出溶媒: 20%酢酸エチル-クロロホルム)で精製して標 20  
題化合物1.53gを得た。

【0059】m. p. 230~232°C

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  ppm; 1.20 (3H, t,  $J=7\text{Hz}$ ), 2.08 (2H, sext,  $J=7\text{Hz}$ ), 2.62 (3H, s), 4.03 (3H, s), 4.33 (2H, t,  $J=7\text{Hz}$ ), 7.19 (1H, d,  $J=8\text{Hz}$ ), 8.39 (1H, dd,  $J=2, 8\text{Hz}$ ), 9.39 (1H, d,  $J=2\text{Hz}$ ), 10.72 (1H, bs).

#### 【0060】実施例3

6-(5-アミノ-2-プロポキシフェニル)-4, 5-ジヒドロ-1, 3-ジメチル-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン 30  
塩化ニッケル1.00g (2.0当量)のメタノール10ml溶液に4, 5-ジヒドロ-1, 3-ジメチル-6-(5-ニトロ-2-プロポキシフェニル)-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン0.72gのテトラヒドロフラン20ml溶液を加え、氷冷下、水素化ホウ素ナトリウム0.31g (4.0当量)を少しずつ加えた。反応溶液を1時間攪拌した後、溶媒を減圧留去した。残留物を希塩酸に加熱溶解し、次いでアンモニア水を加えて溶液のpHを8.0に調節した。クロロホルムで抽出し、乾燥して溶媒を減圧留去して標 40  
題化合物0.57gを得た。このものは精製せずに次の反応に用いた。

【0061】 $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  ppm; 1.20 (3H, t,  $J=7\text{Hz}$ ), 1.97 (3H, t,  $J=7\text{Hz}$ ), 2.60 (3H, s), 3.97 (3H, s), 4.10 (2H, t,  $J=7\text{Hz}$ ), 6.8~7.0 (2H, m), 7.86 (1H, d,  $J=3\text{Hz}$ )

z), 11.21 (1H, bs).

#### 【0062】実施例4

4, 5-ジヒドロ-1, 3-ジメチル-6-[5-(フェノキシカルボニルアミノ)-2-プロポキシフェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン  
6-(5-アミノ-2-プロポキシフェニル)-4, 5-ジヒドロ-1, 3-ジメチル-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン0.48gの塩化メチレン20ml溶液にトリエチルアミン0.23g (1.5当量)を加え、氷冷下クロロギ酸フェニル0.36g (1.5当量)滴下した。反応溶液を室温で3時間攪拌した後、水にあげ、クロロホルムで抽出した。乾燥後、溶媒を減圧留去して、酢酸エチル-ヘキサンで結晶化させて標題化合物0.51gを得た。このものは精製せずに次の反応に用いた。

【0063】 $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  ppm; 1.17 (3H, t,  $J=7\text{Hz}$ ), 2.01 (2H, sext,  $J=7\text{Hz}$ ), 2.61 (3H, s), 3.98 (3H, s), 4.19 (2H, t,  $J=7\text{Hz}$ ), 7.0~7.5 (7H, m), 7.83 (1H, dd,  $J=3, 9\text{Hz}$ ), 8.44 (1H, d,  $J=3\text{Hz}$ ), 11.10 (1H, s).

#### 【0064】実施例5

4, 5-ジヒドロ-1, 3-ジメチル-6-[5-(モルホリノカルボニルアミノ)-2-プロポキシフェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン  
4, 5-ジヒドロ-1, 3-ジメチル-6-[5-(フェノキシカルボニルアミノ)-2-プロポキシフェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン300mgとモルホリン185mg (3.0当量)のN, N-ジメチルホルムアミド20ml溶液を80°Cで3時間攪拌した。反応溶液を水にあげ、酢酸エチルで抽出した。乾燥後、溶媒を減圧留去して残留物をシリカゲルカラムクロマトグラフィー(溶出溶媒: 酢酸エチル)で精製して標題化合物267mgを得た。

【0065】m. p. 244~246°C

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  ppm; 1.12 (3H, t,  $J=7\text{Hz}$ ), 1.93 (2H, sext,  $J=7\text{Hz}$ ), 2.59 (3H, s), 3.56 (4H, t,  $J=5\text{Hz}$ ), 3.78 (4H, t,  $J=5\text{Hz}$ ), 3.91 (3H, s), 4.12 (2H, t,  $J=7\text{Hz}$ ), 6.82 (1H, s), 7.00 (1H, d,  $J=9\text{Hz}$ ), 7.81 (1H, dd,  $J=3, 9\text{Hz}$ ), 8.17 (1H, d,  $J=3\text{Hz}$ ), 11.09 (1H, bs).

#### 【0066】実施例6

4, 5-ジヒドロ-1, 3-ジメチル-6-[5-(ペリジノカルボニルアミノ)-2-プロポキシフェニル]

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ル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン

実施例5と同様にして4, 5-ジヒドロ-1, 3-ジメチル-6-[5-(フェノキシカルボニルアミノ)-2-プロポキシフェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オンとビペリジンから標題化合物を得た。

[0067] m. p. 232~234°C

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.14 (3H, t, J=7Hz), 1.6~1.8 (6H, m), 1.96 (2H, sext, J=7Hz), 2.60 (3H, s), 3.4~3.6 (4H, m), 3.93 (3H, s), 4.13 (2H, t, J=7Hz), 6.58 (1H, s), 6.98 (1H, d, J=9Hz), 7.79 (1H, dd, J=3, 9Hz), 8.15 (1H, d, J=3Hz), 11.07 (1H, s)。

[0068] 実施例7

6-[5-[(4-カルベトキシビペリジノ)カルボニルアミノ]-2-プロポキシフェニル]-4, 5-ジヒドロ-1, 3-ジメチル-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン

実施例5と同様にして4, 5-ジヒドロ-1, 3-ジメチル-6-[5-(フェノキシカルボニルアミノ)-2-プロポキシフェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オンとイソニベコチン酸エチルから標題化合物を得た。

[0069] m. p. 205~207°C

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.13 (3H, t, J=7Hz), 1.27 (3H, t, J=7Hz), 1.7~2.1 (6H, m), 2.4~2.6 (1H, m), 2.59 (3H, s), 3.0~3.2 (2H, m), 3.88 (3H, s), 4.0~4.2 (6H, m), 6.74 (1H, s), 6.97 (1H, d, J=9Hz), 7.76 (1H, dd, J=3, 9Hz), 8.12 (1H, d, J=3Hz), 11.02 (1H, bs)。

[0070] 実施例8

1, 3-ジメチル-5-(2-エトキシ-5-ニトロベンズアミド)-1H-ピラゾール-4-カルボキサミド  
実施例1と同様にして4-アミノ-1, 3-ジメチル-1H-ピラゾール-4-カルボキサミドと2-エトキシ-5-ニトロベンゾイルクロライドから標題化合物を得た。

[0071] m. p. 191~193°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm: 1.44 (3H, t, J=7Hz), 2.30 (3H, s), 3.63 (3H, s), 4.39 (2H, q, J=7Hz), 6.70 (1H, bs), 7.20 (1H, bs), 7.45 (1H, d, J=8Hz), 8.42 (1H, dd, J=2, 8Hz), 8.56 (1H, d, J=2

16

Hz), 10.44 (1H, s)。

[0072] 実施例9

4, 5-ジヒドロ-1, 3-ジメチル-6-(2-エトキシ-5-ニトロフェニル)-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン

実施例2と同様にして1, 3-ジメチル-5-(2-エトキシ-5-ニトロベンズアミド)-1H-ピラゾール-4-カルボキサミドから標題化合物を得た。

[0073] m. p. 266~268°C

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.67 (3H, t, J=7Hz), 2.61 (3H, s), 4.03 (3H, s), 4.45 (2H, q, J=7Hz), 7.18 (1H, d, J=8Hz), 8.39 (1H, dd, J=2, 8Hz), 9.38 (1H, d, J=2Hz), 10.71 (1H, bs)。

[0074] 実施例10

6-(5-アミノ-2-エトキシフェニル)-4, 5-ジヒドロ-1, 3-ジメチル-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン

実施例3と同様にして4, 5-ジヒドロ-1, 3-ジメチル-6-(2-エトキシ-5-ニトロフェニル)-1H-ピラゾロ[3, 4-d]ピリミジン-4-オンから標題化合物を得た。

[0075] <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.54 (3H, t, J=7Hz), 2.60 (3H, s), 3.66 (2H, bs), 3.96 (3H, s), 4.20 (2H, q, J=7Hz), 6.8~7.0 (2H, m), 7.84 (1H, d, J=2Hz), 11.20 (1H, bs)。

[0076] 実施例11

4, 5-ジヒドロ-1, 3-ジメチル-6-[2-エトキシ-5-(フェノキシカルボニルアミノ)フェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン

実施例4と同様にして6-(5-アミノ-2-エトキシフェニル)-4, 5-ジヒドロ-1, 3-ジメチル-1H-ピラゾロ[3, 4-d]ピリミジン-4-オンとクロロ酸フェニルから標題化合物を得た。

[0077] <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.59 (3H, t, J=7Hz), 2.61 (3H, s), 3.98 (3H, s), 4.30 (2H, q, J=7Hz), 7.0~7.5 (7H, m), 7.83 (1H, dd, J=2, 8Hz), 8.43 (1H, d, J=2Hz), 11.07 (1H, s)。

[0078] 実施例12

4, 5-ジヒドロ-1, 3-ジメチル-6-[2-エトキシ-5-(モルホリノカルボニルアミノ)フェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン

実施例5と同様にして4, 5-ジヒドロ-1, 3-ジメチル-6-[2-エトキシ-5-(フェノキシカルボニルアミノ)フェニル]-1H-ピラゾロ[3, 4-d]



ピリミジン-4-オンとモルホリンから標題化合物を得た。

【0079】m. p. 243~245°C

<sup>1</sup>H-NMR (CDC1<sub>3</sub>) δ ppm; 1.55 (3H, t, J=7Hz), 2.61 (3H, s), 3.55 (4H, t, J=5Hz), 3.78 (4H, t, J=5Hz), 3.95 (3H, s), 4.26 (2H, q, J=7Hz), 6.70 (1H, s), 7.01 (1H, d, J=9Hz), 7.81 (1H, dd, J=3, 9Hz), 8.21 (1H, d, J=3Hz), 11.11 (1H, bs)。

【0080】実施例13

4, 5-ジヒドロ-1, 3-ジメチル-6-[2-エトキシ-5-(ビベリジノカルボニルアミノ)フェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン  
実施例5と同様にして4, 5-ジヒドロ-1, 3-ジメチル-6-[2-エトキシ-5-(フェノキシカルボニルアミノ)フェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オンとビベリジンから標題化合物を得た。

【0081】m. p. 227~230°C

<sup>1</sup>H-NMR (CDC1<sub>3</sub>) δ ppm; 1.57 (3H, t, J=7Hz), 1.6~1.8 (6H, m), 2.59 (3H, s), 3.4~3.6 (4H, m), 3.95 (3H, s), 4.25 (2H, q, J=7Hz), 6.50 (1H, bs), 6.99 (1H, d, J=9Hz), 7.80 (1H, dd, J=3, 9Hz), 8.16 (1H, d, J=3Hz), 11.03 (1H, bs)。

【0082】実施例14

6-[5-[(4-カルベトキシビベリジノ)カルボニルアミノ]-2-エトキシフェニル]-4, 5-ジヒドロ-1, 3-ジメチル-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン

実施例5と同様にして4, 5-ジヒドロ-1, 3-ジメチル-6-[2-エトキシ-5-(フェノキシカルボニルアミノ)フェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オンとイソニベコチン酸エチルから標題化合物を得た。

【0083】m. p. 124~127°C

<sup>1</sup>H-NMR (CDC1<sub>3</sub>) δ ppm; 1.27 (3H, t, J=7Hz), 1.57 (3H, t, J=7Hz), 1.8~2.1 (4H, m), 2.5~2.7 (1H, m), 2.59 (3H, s), 3.0~3.2 (2H, m), 3.95 (3H, s), 4.0~4.1 (2H, m), 4.16 (2H, q, J=7Hz), 4.26 (2H, q, J=7Hz), 6.51 (1H, s), 7.01 (1H, d, J=9Hz), 7.77 (1H, dd, J=3, 9Hz), 8.17 (1H, d, J=3Hz), 11.05 (1H, bs)。

【0084】実施例15

4, 5-ジヒドロ-1, 3-ジメチル-6-[2-エトキシ-5-(ピロリジノカルボニルアミノ)フェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン  
実施例5と同様にして4, 5-ジヒドロ-1, 3-ジメチル-6-[2-エトキシ-5-(フェノキシカルボニルアミノ)フェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オンとピロリジンから標題化合物を得た。

【0085】m. p. 258~263°C

<sup>1</sup>H-NMR (CDC1<sub>3</sub>) δ ppm; 1.53 (3H, t, J=7Hz), 1.9~2.1 (4H, m), 2.60 (3H, s), 3.4~3.6 (4H, m), 3.96 (3H, s), 4.26 (2H, q, J=7Hz), 6.28 (1H, bs), 7.01 (1H, d, J=9Hz), 7.88 (1H, dd, J=3, 9Hz), 8.20 (1H, d, J=3Hz), 11.08 (1H, bs)。

【0086】実施例16

6-[5-[[ビス(2-ヒドロキシエチル)アミノ]カルボニルアミノ]-2-エトキシフェニル]-4, 5-ジヒドロ-1, 3-ジメチル-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン

実施例5と同様にして4, 5-ジヒドロ-1, 3-ジメチル-6-[2-エトキシ-5-(フェノキシカルボニルアミノ)フェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オンとジエタノールアミンから標題化合物を得た。

【0087】m. p. 210~212°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm; 1.32 (3H, t, J=7Hz), 2.43 (3H, s), 3.4~3.7 (8H, m), 3.83 (3H, s), 4.12 (2H, q, J=7Hz), 5.02 (2H, m), 7.08 (1H, d, J=9Hz), 7.53 (1H, dd, J=3, 9Hz), 7.78 (1H, d, J=3Hz), 8.62 (1H, s), 11.73 (1H, bs)。

【0088】実施例17

4, 5-ジヒドロ-6-[5-[[[(1, 3-ジヒドロキシプロピル)アミノ]カルボニルアミノ]-2-エトキシフェニル]-1, 3-ジメチル-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン

実施例5と同様にして4, 5-ジヒドロ-1, 3-ジメチル-6-[2-エトキシ-5-(フェノキシカルボニルアミノ)フェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オンと2-アミノ-1, 3-プロパンジオールから標題化合物を得た。

【0089】m. p. 260~265°C

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm; 1.32 (3H, t, J=7Hz), 2.44 (3H, s), 3.3

~3.7 (5H, m), 3.83 (3H, s), 4.12 (2H, q, J=7Hz), 4.72 (2H, t, J=5Hz), 5.98 (1H, d, J=8Hz), 7.08 (1H, d, J=9Hz), 7.52 (1H, d, J=3, 9Hz), 7.84 (1H, d, J=3Hz), 8.66 (1H, s), 11.69 (1H, bs)。

#### 【0090】実施例18

4, 5-ジヒドロ-1, 3-ジメチル-6-[2-エトキシ-5-[(4-ヒドロキシベリジン)カルボニルアミノ]フェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン

実施例5と同様にして4, 5-ジヒドロ-1, 3-ジメチル-6-[2-エトキシ-5-(フェノキシカルボニルアミノ)フェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オンと4-ヒドロキシベリジンから標題化合物を得た。

【0091】m. p. 230~232°C

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.57 (3H, t, J=7Hz), 1.6~1.7 (2H, m), 1.9~2.1 (2H, m), 2.59 (3H, s), 3.2~3.2 (2H, m), 3.8~4.1 (3H, m), 3.94 (3H, s), 4.26 (2H, q, J=7Hz), 6.57 (1H, s), 7.01 (1H, d, J=9Hz), 7.78 (1H, dd, J=3, 9Hz), 8.17 (1H, d, J=3Hz), 11.06 (1H, bs)。

#### 【0092】実施例19

4, 5-ジヒドロ-1, 3-ジメチル-6-[2-エトキシ-5-[(4-メチルピペラジン)カルボニルアミノ]フェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン

実施例5と同様にして4, 5-ジヒドロ-1, 3-ジメチル-6-[2-エトキシ-5-(フェノキシカルボニルアミノ)フェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オンとN-メチルピペラジンから標題化合物を得た。

【0093】m. p. 185~190°C

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.53 (3H, t, J=7Hz), 2.37 (3H, s), 2.50 (2H, m), 2.58 (3H, s), 3.58 (2H, m), 3.88 (3H, s), 4.21 (2H, q, J=7Hz), 6.76 (1H, s), 6.96 (1H, d, J=9Hz), 7.77 (1H, dd, J=3, 9Hz), 8.12 (1H, d, J=3Hz), 11.00 (1H, bs)。

#### 【0094】実施例20

4, 5-ジヒドロ-1, 3-ジメチル-6-[2-プロポキシ-5-(チオモルホリノカルボニルアミノ)フェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-

#### -オン

実施例5と同様にして4, 5-ジヒドロ-1, 3-ジメチル-6-[5-(フェノキシカルボニルアミノ)-2-プロポキシフェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オンとチオモルホリンから標題化合物を得た。

【0095】m. p. 249~252°C

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.13 (3H, t, J=7Hz), 1.95 (2H, sext, J=7Hz), 2.59 (3H, s), 2.6~2.8 (4H, m), 3.8~3.9 (4H, m), 3.88 (3H, s), 4.11 (2H, t, J=7Hz), 6.70 (1H, s), 6.98 (1H, d, J=9Hz), 7.76 (1H, dd, J=3, 9Hz), 8.12 (1H, d, J=3Hz), 11.00 (1H, s)。

#### 【0096】実施例21

4, 5-ジヒドロ-1, 3-ジメチル-6-[2-エトキシ-5-(チアゾリジノカルボニルアミノ)フェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン

実施例5と同様にして4, 5-ジヒドロ-1, 3-ジメチル-6-[2-エトキシ-5-(フェノキシカルボニルアミノ)フェニル]-1H-ピラゾロ[3, 4-d]ピリミジン-4-オンとチアゾリジンから標題化合物を得た。

【0097】m. p. 216~218°C

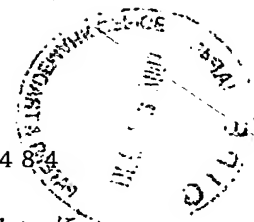
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ ppm: 1.56 (3H, t, J=7Hz), 2.59 (3H, s), 3.14 (2H, t, J=6Hz), 3.85 (2H, t, J=6Hz), 3.91 (3H, s), 4.24 (2H, s), 4.62 (2H, s), 6.57 (1H, s), 7.00 (1H, d, J=9Hz), 7.81 (1H, dd, J=3, 9Hz), 8.19 (1H, d, J=3Hz), 11.01 (1H, bs)。

#### 【0098】実施例22

4, 5-ジヒドロ-1, 3-ジメチル-6-(2-エトキシ-5-ウレイドフェニル)-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン

6-(5-アミノ-2-プロポキシフェニル)-4, 5-ジヒドロ-1, 3-ジメチル-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン400mgの酢酸10ml溶液にシアン酸カリウム520mg(5.0当量)の水5ml溶液を加え、室温で3時間攪拌した。析出した結晶を濾取し、水で洗浄した。得られた結晶を減圧乾燥して標題化合物410mgを得た。

【0099】<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm: 0.96 (3H, t, J=7Hz), 1.73 (2H, sext, J=7Hz), 2.44 (3H, s), 3.84 (3H, s), 4.01 (2H, t, J=7Hz), 5.80 (2H, s), 7.09 (1H, d, J



=9 Hz), 7. 59 (1H, dd, J=3, 9 Hz), 7. 84 (1H, d, J=3 Hz), 8. 58 (1H, s), 11. 64 (1H, bs)。

【0100】実施例 23

6-[5-[(4-カルボキシビベリジノ)カルボニルアミノ]-2-エトキシフェニル]-4, 5-ジヒドロ-1, 3-ジメチル-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン

6-[5-[(4-カルベトキシビベリジノ)カルボニルアミノ]-2-エトキシフェニル]-4, 5-ジヒドロ-1, 3-ジメチル-1H-ピラゾロ[3, 4-d]ピリミジン-4-オン 0. 20 g のメタノール 10 ml 溶液に炭酸カリウム 0. 18 g の水 2 ml 溶液を加え、室温で一晩攪拌した。反応溶液に 10%塩酸を加えて pH 1 とし、析出した結晶を濾過、水で洗浄した後、減圧乾燥して標題化合物 0. 15 g を得た。

【0101】m. p. 232~234℃

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ ppm: 1. 32 (3H, t, J=7 Hz), 1. 4~1. 6 (2H, m), 1. 8~1. 9 (2H, m), 2. 4~2. 6 (1H, m), 2. 43 (3H, s), 2. 8~3. 0 (2H, m), 3. 84 (3H, s), 3. 9~4. 1 (2H, m), 4. 11 (2H, q, J=7 Hz), 7. 09 (1H, d, J=9 Hz), 7. 61 (1H, dd, J=3, 9 Hz), 7. 86 (1H, d, J=3 Hz), 8. 54 (1H, s), 11. 70 (1H, bs)。

【0102】試験例 (ホスホジエステラーゼ阻害作用)  
ホスホジエステラーゼアイソザイムは、犬大動脈可溶成分より Mono QHR5/5 カラムを用いた FRLC システムにて精製した。すなわち、摘出組織を 25 mM トリス塩酸緩衝液、250 mM スクロール、2 mM 塩化マグネシウム、1 mM エチレングリコールビス (β-アミノエチルエーテル) N, N, N', N'-四酢酸、1 mM ジチオスレイトールおよび各種プロテアーゼインヒビターの存在下にてホモジナイズした後、塩勾配によりタンパク質画分の溶出を行い、各画分のホスホジエステラーゼ活性を測定することによりカルシウム・カルモジュリン依存性ホスホジエステラーゼとサイクリック GMP 特異的ホスホジエステラーゼの混合画分を得た。さらに\*

\*カルモジュリアンアフィニティークロマトグラフィーにより両者を分離精製した。

【0103】ホスホジエステラーゼ活性の測定は Biochem. Biophys. Res. Commun., 第 148 巻, 第 1468 頁 (1987 年, S. Matsuhashi ら) に記載された方法に従い、犬大動脈サイクリック GMP 特異的ホスホジエステラーゼについては活性因子として 0. 2 mM エチレングリコールビス (β-アミノエチルエーテル) N, N, N', N'-四酢酸存在下, 0. 4 mM [<sup>3</sup>H] サイクリック GMP を基質として測定した。

【0104】被検薬物は 100% ジメチルスルホキシドに溶解後、10% ジメチルスルホキシド溶液として用いた。反応中の最終濃度は 1% ジメチルスルホキシドとした。

【0105】結果は、表 4 に示す。

【0106】

【表 4】

検 体	IC <sub>50</sub> 値 (nM)
5	2. 4
6	1. 5
7	6. 0
12	3. 4
13	6. 7
14	9. 9
15	14
16	22
18	8. 5
19	24
20	9. 3
21	11
22	29

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